Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: Should current practice be changed?

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Background: Hemodilutional anemia during cardiopulmonary bypass can lead to inadequate oxygen delivery and, consequently, to ischemic organ injury. In adult bypass, the nadir hematocrit can vary widely with body size and prebypass hematocrit variations, yet its effects on perioperative organ dysfunction and patient outcomes remain largely unknown.

Methods: To elucidate these effects, we retrospectively analyzed operative results and resource utilization data from 5000 consecutive cardiac operations with cardiopulmonary bypass performed on adults (1994 to 2000). Rolling decile groups (500 patients each; 75% overlapping) of increasing lowest hematocrit values were used to characterize hemodilution-outcome relationships. Intermediate-term (0 to 6 years) survival was assessed for coronary artery bypass patients (n = 3800) via Kaplan-Meier analysis in quintile subgroups based on lowest hematocrit. Multivariate logistic regression (operative mortality and morbidity) and Cox proportional hazard model (0- to 6-year mortality) analyses were used to determine independent predictors of poor outcomes.

Results: Stroke, myocardial infarction, low cardiac output, cardiac arrest, renal failure, prolonged ventilation, pulmonary edema, reoperation due to bleeding, sepsis, and multiorgan failure were all significantly and systematically increased as lowest hematocrit value decreased below 22%. Consequently, intensive care requirements, hospital stays, operative costs, and operative deaths were also significantly greater as a function of hemodilution severity. Longer-term survival was improved systematically for increasing lowest hematocrit coronary artery bypass grafting quintiles; for example, 6-year survival was 80.5% and 92.3% for quintiles I (lowest hematocrit = 16.1%) and V (lowest hematocrit = 27.5%). The continuous variable lowest hematocrit was an independent predictor of (1) operative mortality, (2) prolonged cardiovascular intensive case (>2 days) and postoperative hospital (>8 days) stays, and (3) worse 0- to 6-year survival.

Conclusions: Increased hemodilution severity during cardiopulmonary bypass was associated with worse perioperative vital organ dysfunction/morbidity and increased resource use, as well as greater short- and intermediate-term mortality. We speculate that these results derive from inadequate oxygen delivery causing ischemic and/or inflammatory vital organ injury, as recently demonstrated intravitally in cerebral tissues. Although this analysis of a large observational study offers evidence linking low on-pump hematocrit values to these adverse outcomes, prospective randomized trials are needed (1) to establish whether a causal effect of hemodilution on poor outcomes actually exists and (2) to test the potential efficacy of maintaining on-pump hematocrit above 22% for improving outcomes of cardiopulmonary bypass.

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The Boston group[1] headed by Jonas recently demonstrated, in an intravital animal model, that perfusion of the cerebral microcirculation is not impaired by high hematocrit value (30%) during cardiopulmonary bypass (CPB) compared with moderate (20%) or low (10%) hematocrit value. They also reported evidence of increasingly inadequate cerebral tissue oxygenation and greater white cell–endothelial activation as hematocrit values during CPB decreased.[1] Finally, the authors proposed that their intravital results of increased ischemia and inflammatory tissue injury with greater hemodilution explained earlier findings of improved neurological outcomes with high hematocrit.[2,3]

Arguably, the above results may have significant implications to current CPB practice as they contradict prevailing cardiac surgical dogma and current recommendations of textbooks[4,5], that is, that lower hematocrit values ($\leq$20%) minimize microcirculatory disturbances during CPB and hence will improve tissue perfusion and oxygen delivery. Additionally, if these findings in the cerebral microcirculation prevail in other capillary beds, then milder hemodilution may similarly lead to improved post-CPB outcomes of other vital organs.

In adult CPB, variations of body size and pre-CPB hematocrit, coupled with the essentially constant bypass circuit volume, inevitably lead to wide interpatient variability of the nadir on-pump hematocrit.[6] The primary objective of this study was to elucidate the effects of varying "lowest hematocrit" during CPB on postoperative organ dysfunction and patient outcomes. We therefore determined in a large contemporary cardiac surgery series (with CPB) the incidence of serious complications, operative mortality, and resource utilization in terms of varying lowest hematocrit. Also, for isolated coronary artery bypass grafting (CABG), we probed whether and how potential adverse effects of lowest hematocrit levels alter long-term outcomes.

Methods

Patients

With approval of the St Vincent Mercy Medical Center (Toledo, Ohio) Human Investigation Committee, we analyzed the clinical outcomes of 5000 consecutive adult cardiac surgery patients from a single institution (1994-2000). Standard CPB techniques were applied with predominant (96%) use of normothermia (body temperature: 35°C to 37°C).[6] Arterial blood flow was determined on the basis of a cardiac index of 2.5 to 3.0 ($L \cdot min^{-1} \cdot m^{-2}$), and mean arterial pressure was maintained at greater than 60 mm Hg. All surgeons used standardized clinical care pathway protocols.

Data Collection

Risk factors, CPB variables, complications, and operative mortality (OM; in-hospital death or <30 days out-of-hospital death) data were collected in a dedicated database. Cardiovascular intensive care unit (CVICU) and postoperative length of stays (LOS) were entered for all patients in the same database. Total direct variable costs (Cost) were compiled for patients from 1997 to 2000, and these encompassed every care-related expense throughout the admission period.[7] Cost data are presented in terms of the annual average cost to correct for inflation.

The social security death index database (http://ssdi.geneology.rootsweb.com) was queried in October 2001 for each patient via individual searches to verify accurate out-of-hospital death data. This resulted in survival follow-up data for all patients ranging from up to 8 to 93 months. Our database was updated for any missing late mortality data.

Data Analysis/Statistical Methods

Univariate analyses. Lowest hematocrit is a continuous normally distributed variable, and examining its effects on "dichotomous" outcome measures (eg, mortality [yes/no]) can hinge on how the population is subdivided.[6] Multiple steps were applied to identify outcomes associated to the extent of hemodilution on CPB. First, mean lowest hematocrit values of each complicated subgroup (eg, stroke) were compared with patients free of any complications. Next, incidence of each complication was compared among lowest hematocrit quintile groups (n = 1000 each). Finally, we derived continuous independent variable–outcome relations by consideration of rolling decile subgroups.[6] Here, patient data were first arranged in increasing lowest hematocrit order, and a total of 37 subgroups (75% overlapping ranges) were separately analyzed, such that group 1 included patients 1 to 500 (0%-10%), group 2 included patients 126 to 625 (2.5%-12.5%), and so on. Note, with this method, the smaller subgroup size minimized within-group lowest hematocrit heterogeneity while the 75% overlap smoothed the effects of similar lowest hematocrit values in consecutive subgroups.

Continuous variables were presented as mean $\pm$ standard deviation and categorical data were presented as frequency counts (N, %). Nonlinear regression analyses (SPSS, Inc, Chicago, Ill) were used to describe continuous lowest hematocrit–outcome relations. Group comparisons of continuous variables were done using unpaired *t* test (2 groups) or 1-way analysis of variance (3 or more groups) depending on applicability. χ^2-Square tests were used for categorical variables. Long-term survival was assessed via Kaplan-Meier and death hazard analyses.[8]

Multivariate analyses. We used multivariate analyses to determine if and how nadir on-pump hematocrit, among other variables, predicted certain outcomes (length of stay as well as early and late mortality). Also, we determined the pre- and intraoperative variables predicting the extent of hemodilution on CPB, or lowest hematocrit (%), via multiple linear regression analysis (SPSS). All multivariate methods were limited to the 3800 patients who underwent isolated CABG to avoid the possible varying effects on outcomes of valve and or combined operations.

First, predictors of operative mortality and perioperative morbidity were derived via multiple logistic regression (SPSS). We defined perioperative morbidity as patients who remained in excess of 48 hours in cardiovascular intensive care (CVICU > 2 days) or patients with postoperative hospital stays greater than 8 days. Cox proportional hazard models were used to define the effect of explanatory variables (including lowest hematocrit) on 0- to 6-year mortality after CABG with CPB. Model selection was

TABLE 1. Demographics, risk factors, and cardiopulmonary bypass data for all patients and for quintiles (I–V) divided based on lowest hematocrit

	All patients		Lowest hematocrit subgroups* (No. = 1000)					
Category	Mean ± SD/n	%	I	II	III	IV	V	*P* value
Females	1704	34.0	70.3	50.0	29.6	15	4.4	<.001
Age (years)	64 ± 11		67 ± 11	66 ± 11	65 ± 11	63 ± 10	60 ± 11	<.001
Body surface area (m^2)	1.96 ± 0.23		1.79 ± 0.19	1.89 ± 0.20	1.96 ± 0.19	2.04 ± 0.19	2.13 ± 0.19	<.001
Diabetes	1562	31.2	35.6	34.6	29.8	27.6	28.6	<.001
Renal failure	171	3.4	8.0	4.6	2.3	1.6	0.6	<.001
Cerebrovascular accident	416	8.3	11.1	9.3	8.6	6.1	6.5	<.001
COPD	1110	22.3	22.6	22.0	22.5	22.2	22.2	NS
Peripheral vascular disease	839	16.8	21.2	19.4	16.3	15.4	11.6	<.001
Left main disease	895	18.2	19.5	19.1	17.4	16.8	18.0	NS
Three vessel disease	3173	63.4	61.2	62.4	63.5	65.5	64.2	NS
Ejection fraction (%)	49 ± 12		50 ± 12	49 ± 12	50 ± 12	49 ± 12	49 ± 11	NS
Isolated CABG	3800	76.0	67	72	76.9	78.9	84.6	<.001
Redo Surgery	345	7.2	8.8	8.8	6.6	8.1	3.6	<.001
Nonelective	2807	56.1	62.5	57.6	53.2	51.6	55.7	<.001
Time on CPB (min)	95 ± 47		106 ± 59	98 ± 51	93 ± 44	91 ± 39	85 ± 36	<.001
Pre-CPB hematocrit (%)	37.8 ± 5.4		32.9 ± 4.4	35.4 ± 4.4	38.0 ± 4.1	40.1 ± 4.2	42.6 ± 3.7	<.001
Lowest hematocrit (%)	21.4 ± 4.2		15.9 ± 1.4	18.9 ± 0.7	21.3 ± 0.7	23.6 ± 0.8	27.5 ± 2.1	<.001
Post-CPB hematocrit (%)	23.5 ± 4.2		19.7 ± 3.4	21.1 ± 2.7	22.8 ± 2.8	25.1 ± 1.9	29 ± 2.6	<.001
Intraoperative transfusion	1305	26.1	66.6	32.8	17.1	10.3	3.6	<.001

*Quintile data presented either as mean ± SD (standard deviation) or as % incidence. Statistical comparisons were done using one-way analysis of variance or Chi-square test as applicable. *CABG,* coronary artery bypass grafting; *COPD,* chronic obstructive pulmonary disease; *n* = number of patients or frequency; *NS* = differences between quintile groups are not significant.

first done with backward elimination and variables significant at the $P < .05$ level were retained in the model as independent predictors. Models were then confirmed using forward selection and stepwise selection. The considered prognostic variables in the multivariate models were the preoperative and intraoperative variables listed in Table 1 in addition to the categorical variables postoperative transfusion and use of intra-aortic balloon pump.

Results

This CPB series (64 ± 11 years) included 3296 (66%) men and 1704 (34%) women (Table 1). Of these, 3800 underwent isolated CABG (76%). The lowest hematocrit value reached during CPB varied widely among patients (21.4 ± 4.2%, median = 21.2%, range: 9.1%-40.3%). Lowest hematocrit quintiles show that older age, female sex, diabetes, history of cerebrovascular accidents, preoperative renal failure, peripheral vascular disease, non-CABG, reoperation, nonelective status, and increased time on bypass were all more frequent in more hemodiluted patients (Table 1). Alternatively, ejection fraction, chronic obstructive pulmonary disease, left main disease, and three-vessel disease did not vary with this on-pump hematocrit level.

Independent predictors of the nadir hematocrit determined via multivariate linear regression included four continuous (pre-CPB hematocrit value, body surface area, time on CPB, and age) and two categorical (female sex and preoperative renal failure) variables (Table 2). Pre-CPB hematocrit value (%) and body surface area (BSA) were the

TABLE 2. Predictors of lowest hematocrit (%) during CPB derived by forward stepwise multivariate linear regression

Variable	Coefficient (a_1–a_6)	Std Error	*P* value	R	ΔR^2 (%)
Pre-CPB Hct (%)	0.390	0.010	<.001	0.660	73.4
BSA (m^2)	5.467	0.235	<.001	0.740	18.9
Time on CPB (min)	−0.022	0.001	<.001	0.760	5.1
Female	−1.327	0.115	<.001	0.769	2.3
Age (years)	−0.017	0.004	<.001	0.770	<0.3
Renal failure	−0.825	0.268	.002	0.771	<0.2

Model: lowest hematocrit (%) = a_1*Pre-CPB Hct (%) + a_2*BSA (m^2) + a_3*Time on CPB (min) + a_4*Female + a_5*Age (years) + a_6*renal failure. Model passed normality ($P = .89$) and constant variance ($P = .012$) tests; power ($\alpha = 0.05$) = 1.0; female and renal failure are categorical variables where yes = 1 and no = 0.

main determinants of the nadir hematocrit on pump as would be expected based on red blood cell mass balance considerations in conjunction with a constant volume of the CPB crystalloid prime. Alternatively the variations in lowest hematocrit value in terms of age and time on CPB are probably indirect, and reflect (1) the on-average lower pre-CPB hematocrit value (39%-35%) and BSA (2.0-1.8 m^2) with increasing CABG patient age (60-80 years) and (2) greater blood loss with prolonged pump times.

A total of 181 operative deaths (3.6%) patients were documented in this 5000 CPB patient series, and 975 pa-

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tients had at least one postoperative complication (19.5%). For the 3800 CABG only patients in this series, as of October 2001, 355 (9.3%) patients were dead (OM: 90 or 2.4%; late: 265 or 6.9%). Time to death was 20 ± 21 months (median = 10; range: 0-79) and follow-up was 53 ± 23 (median = 53, range: 8-93) months.

Effects of Lowest Hematocrit on Outcomes

Operative outcomes. Variations in hemodilution levels for patients, which were divided based on incidence of postoperative complications, are summarized in Table 3. Lowest hematocrit for OM (19.0 ± 4.1%) and complicated (19.9 ± 4.0%) patients were significantly lower than for uncomplicated (21.8 ± 4.1%) patients (unpaired *t* test). Moreover, this trend was true for all types of complications, and more severe hemodilution was associated with greater likelihood of multiple complications.

Consistent with the above, analysis of lowest hematocrit based quintiles (Table 4) shows that all measures of morbidity, except for sternal wound infection and acute respiratory distress syndrome, change systematically with the extent of hemodilution (1-way analysis of variance). In brief, for all CPB as well as for isolated CABG (Figure 1), the incidence of reoperation for bleeding (~fivefold), tamponade (~sixfold), perioperative myocardial infarction (~fourfold), cardiac arrest (~fourfold), permanent stroke (~sixfold), coma (~sixfold), prolonged mechanical ventilation (~threefold), pulmonary edema (~fourfold), septicemia (~threefold), use of intra-aortic balloon pump (~fourfold), renal failure (~fourfold), and multiorgan failure (~sevenfold) were all systematically greater as lowest hematocrit value decreased. Note, adverse hemodilution effects were particularly greater for lowest hematocrit value below 22%.

Consequently, CVICU/postoperative LOS and OM varied substantially with lowest hematocrit value (Figure 2). Both hospital stays and OM were generally lower for (1) CABG versus non-CABG patients and (2) younger (≤65 years) versus older (>65 years) patients. Yet, their decreasing trends as lowest hematocrit increased were similar. Multivariate predictors of operative mortality and morbidity (CVICU > 2 days, postoperative LOS > 8 days) as determined by multivariate logistic regression are summarized in Table 5. This analysis showed that, along with other predictors, decreased lowest hematocrit value (%; considered as a continuous variable) is associated with (1) increased operative mortality (risk ratio: 0.863; $P < .001$), (2) increased likelihood of prolonged intensive care stay (CVICU > 2 days; risk ratio: 0.968; $P < .001$), and (3) greater likelihood of postoperative hospitalization of 9 or more days (postoperative LOS >8 days; risk ratio: 0.954; $P < .001$).

Frequency of intraoperative and postoperative transfusion and the direct variable costs of surgery were strongly related to the severity of hemodilution (Figure 3). Note, the effects of hemodilution on average operative costs were similar for all CPB surgeries or CABG only, and these increased sharply for lowest hematocrit < 20%, while they were unchanged for lowest hematocrit value >24%.

Longer-term outcomes. For all isolated CABG patients combined, the 1-, 3-, and 6-year survival estimates were 95.2%, 92.5%, and 88.1%, respectively. However, longer-term (0-6 years) effects of decreased lowest hematocrit value were also apparent in isolated CABG patients. When separately analyzed, lowest hematocrit value (16.1%-27.5%) CABG quintiles (760 patients each) exhibited increasingly better survival (1-year: 90.1%-97.6%; 3-year: 86.1%-96.0%; and 6-year: 80.5%-92.3%) with decreasing hemodilution severity (Figure 4, *top*). Moreover, death hazard analysis of the Kaplan-Meier survival curves for CABG patients divided to lowest hematocrit ≤20% (N = 1418) versus >20% (N = 2382) shows systematically greater

TABLE 3. Variations in lowest hematocrit on CPB for complicated patient groups

Patient group	Mean ± SD	Median	*P* value
All patients	21.4 ± 4.2	21.2	
Operative mortality	19.0 ± 4.1	18.5	<.001
Postop complication			
No (4025; 80.5%)	21.8 ± 4.1	21.8	Ref.
Yes (975; 19.5%)	19.9 ± 3.9	19.4	<.001
One (451; 9.0%)	20.4 ± 3.7	20.0	<.001
Two (251; 5.0%)	19.7 ± 4.0	19.1	<.001
Three or more (273; 5.5%)	19.4 ± 4.0	19.1	<.001
Reoperation for bleeding	19.5 ± 3.9	19.1	<.001
Infection	20.3 ± 3.9	19.7	<.001
Sternal wound infection	20.8 ± 3.6	20.0	<.07
Septicemia	20.0 ± 4.0	19.4	<.001
Neurologic	19.6 ± 4.0	19.1	<.001
Transient stroke	20.2 ± 3.8	20.0	<.001
Permanent stroke	19.2 ± 4.1	18.8	<.001
Coma	18.9 ± 3.2	18.8	<.001
Pulmonary	19.7 ± 4.0	19.1	<.001
Prolonged ventilation	19.6 ± 4.0	19.1	<.001
Pulmonary edema	19.4 ± 3.7	19.1	<.001
ARDS	20.3 ± 3.9	20.6	<.02
Cardiac	19.5 ± 4.0	19.1	<.001
Perioperative MI	19.5 ± 4.2	19.4	<.001
Tamponade	19.3 ± 3.5	19.4	<.001
Cardiac arrest	19.2 ± 4.1	18.5	<.001
Intra/postop IABP	19.5 ± 4.0	18.8	<.001
Renal failure	19.9 ± 3.8	19.7	<.001
Multiorgan failure	19.2 ± 3.9	18.5	<.001

All statistical comparisons of lowest hematocrit (%) for the various complication/mortality subpopulations were done using the unpaired *t* test where the patients with no postop complications were used as the reference population (referred to as *Ref.* in the table). *ARDS,* acute respiratory distress syndrome; *IABP,* intra-aortic balloon pump; *MI,* myocardial infarction; *n* = number of patients with complication; *Ref,* reference or statistical control; *SD,* standard deviation.

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TABLE 4. Postoperative data for all patients and for quintiles (I–V) divided based on lowest hematocrit

	All patients		Lowest hematocrit subgroups* (N_Q = 1000)					
Category	Mean ± SD/n	%	I	II	III	IV	V	*P* value
Postoperative transfusion	1691	33.8	55.7	46.0	32.0	23.0	12.3	<.001
Reoperation for bleeding	145	2.9	5.1	3.6	3.0	1.6	1.2	<.001
Sternal wound infection	69	1.4	1.5	2.0	1.4	1.1	0.9	NS
Septicemia	103	2.1	2.9	2.9	1.7	1.6	1.2	<.02
Transient stroke	63	1.3	2.0	1.2	1.3	1.2	0.6	.09
Permanent stroke	95	1.9	3.4	2.5	1.2	1.7	0.7	<.001
Coma	54	1.1	1.8	2.0	0.7	0.7	0.2	<.001
Prolonged ventilation	450	9.0	15.3	12.1	6.6	6.4	4.6	<.001
Pulmonary edema	138	2.8	4.8	4.4	1.9	1.6	1.1	<.001
ARDS	52	1.0	1.4	1.1	0.8	1.2	0.7	NS
Perioperative MI	55	1.1	1.9	1.5	0.8	0.8	0.5	<.02
Tamponade	42	0.8	1.3	1.3	1.0	0.3	0.3	<.02
Cardiac arrest	163	3.3	6.2	4.6	1.7	2.5	1.3	<.001
Intra/postoperative IABP	224	4.5	9.1	4.1	3.9	3.2	2.1	<.001
Renal failure	294	5.9	7.9	8.5	5.7	4.9	2.4	<.001
Multiorgan failure	93	1.9	3.4	2.8	1.1	1.3	0.7	<.001
Operative mortality	181	3.6	7.5	4.7	1.8	2.5	1.6	<.001
CVICU stay (days)	1.7 ± 3.0		2.0 ± 3.2	2.1 ± 3.8	1.5 ± 2.4	1.5 ± 2.7	1.3 ± 2.3	<.001
Postoperative LOS (days)	7.6 ± 9.1		9.5 ± 11.1	8.6 ± 10.8	7.7 ± 9.8	6.5 ± 6.6	6.0 ± 5.6	<.001

ARDS, Acute respiratory distress syndrome; *CVICU,* cardiovascular intensive care unit; *IABP,* intra-aortic balloon pump; *LOS,* length of stay; *MI,* myocardial infarction; *n,* number of patients or frequency; *NS,* differences between quintile groups are not significant.
*Quintile data presented either as mean ± SD (standard deviation) or as % incidence. Statistical comparisons were done using one-way analysis of variance or Chi-square test as applicable.

early as well as late mortality in the more severely hemodiluted group (Figure 4, *bottom*).

Results of multivariate Cox proportional hazard model analysis of 0- to 6-year mortality are summarized in Table 6. These showed that decreased lowest hematocrit value (%) is associated with worse survival over this interval (odds ratio: 0.950; $P = .001$). Other predictors of 0- to 6-year mortality were older age (years), increased time on cardiopulmonary bypass (minutes), lower ejection fraction (%), in addition to four other categorical (yes/no) variables/diagnoses: preoperative renal failure, chronic lung disease, cerebrovascular disease, and peripheral vascular disease.

Discussion

We demonstrated, via a large consecutive adult cardiac surgery series, that adverse outcomes after CPB are systematically increased as a function of hemodilution severity. Specifically, we showed that most major complications, including stroke, myocardial infarction, low cardiac output syndrome (intraoperative/postoperative intra-aortic balloon pump), renal failure, pulmonary edema, reoperation due to bleeding, sepsis, and multiorgan failure, are increased as the nadir hematocrit during CPB decreased (Figure 1). Moreover, this hematocrit–complications association inevitably resulted in significantly and systematically greater intensive care requirements, hospital stays, operative costs, and death with increasing levels of hemodilution, particularly for lowest hematocrit value less than 22% (Figures 3 and 4). Indeed, the observed-to-expected (O/E) CABG mortality decreased systematically and substantially for patient cohorts whose lowest hematocrit was between 15% and 22% and was relatively unchanged for greater values (Figure 3, *bottom right*). Lowest hematocrit value (%) was also found to be an independent predictor of operative mortality and morbidity (Table 5).

In addition, somewhat unexpectedly, we found that hemodilutional anemia on bypass was associated with long-term adverse effects as well. Specifically, survival trends of lowest hematocrit CABG quintile subgroups (I to V: 760 patients each) were significantly and systematically better with decreasing hemodilution severity (Figure 4). For example, 6-year survival was 80.5% for group I patients in whom the average lowest hematocrit value was a low 16.1%. In contrast, groups IV (lowest hematocrit value: 23.6%) and V (lowest hematocrit: 27.5%) both had a 92.3% survival 6 years after CABG. Granted, systematically younger age of patients for group I (67 years) through group V (60 years) and the fact that operative deaths were also greater in the more hemodiluted patients have contributed to the difference in survival. However, this lowest hematocrit effect on intermediate-term survival that is apparent from 0- to 6-year survival and death hazard analyses in CABG patients (Figure 4) was confirmed to be an independent predictor by multivariate Cox proportional hazard analysis (Table 6).

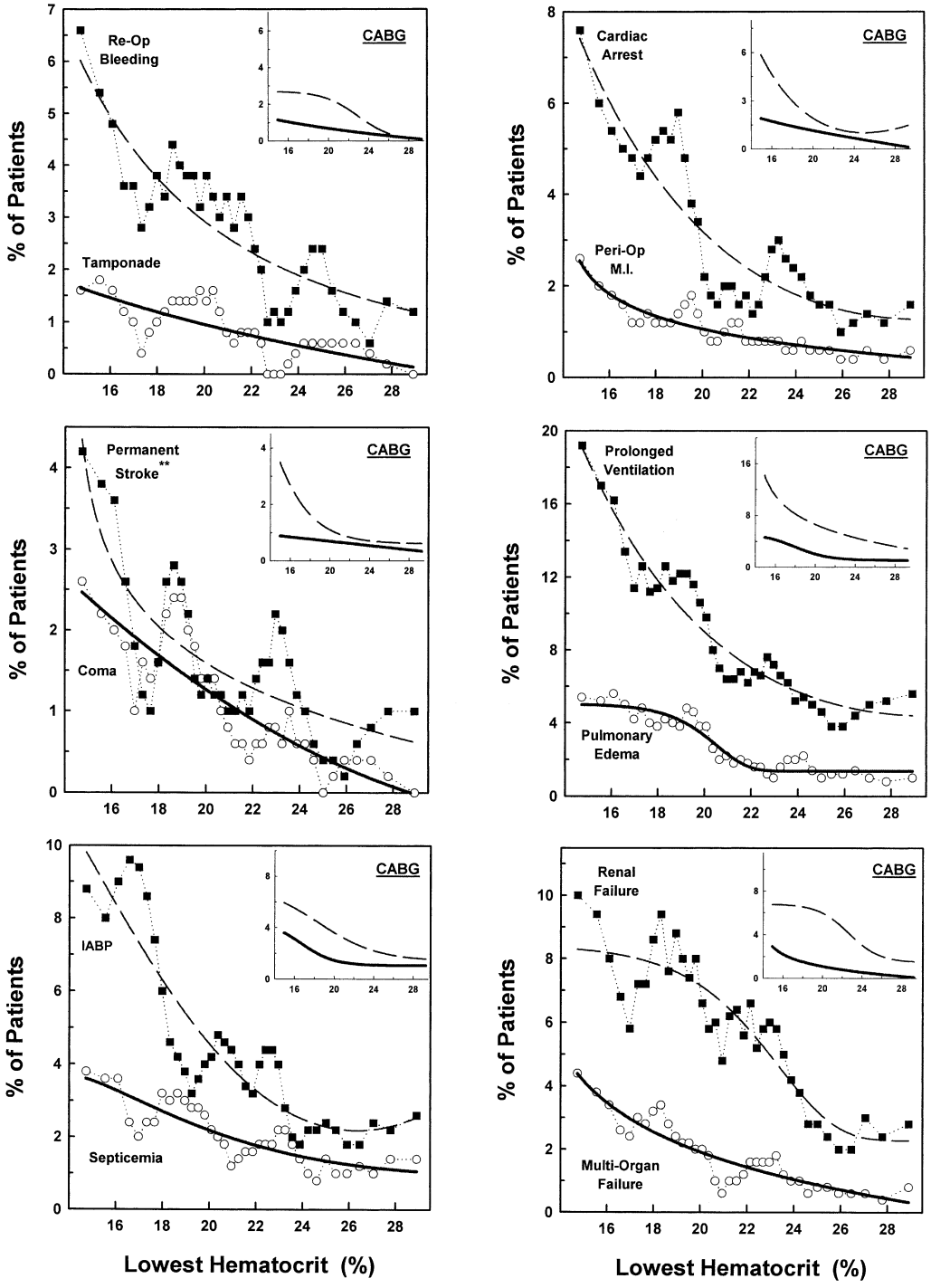

Figure 1. Incidence of 12 postoperative complications (see specific complication on each plot) reflecting the dysfunction post-CPB of the various vital organs shown plotted in terms of increasing lowest hematocrit for all cardiac surgeries (n = 5000 patients). All types of complications were more frequent as hemodilution severity increased, particularly for lowest hematocrit < 22%. *Lines* (*solid* and *dashed*) represent nonlinear regression approximations of actual trends shown for rolling decile groups as *symbols* (*open* and *closed*, respectively). These trends were similar (albeit not in magnitude) when only isolated CABG patients (n = 3800) are considered (symbols were omitted for clarity). Generally lower incidence of complications in CABG compared to all cardiac operations suggest higher incidence of complications in non-CABG operations with perhaps greater adverse effects of hemodilution.

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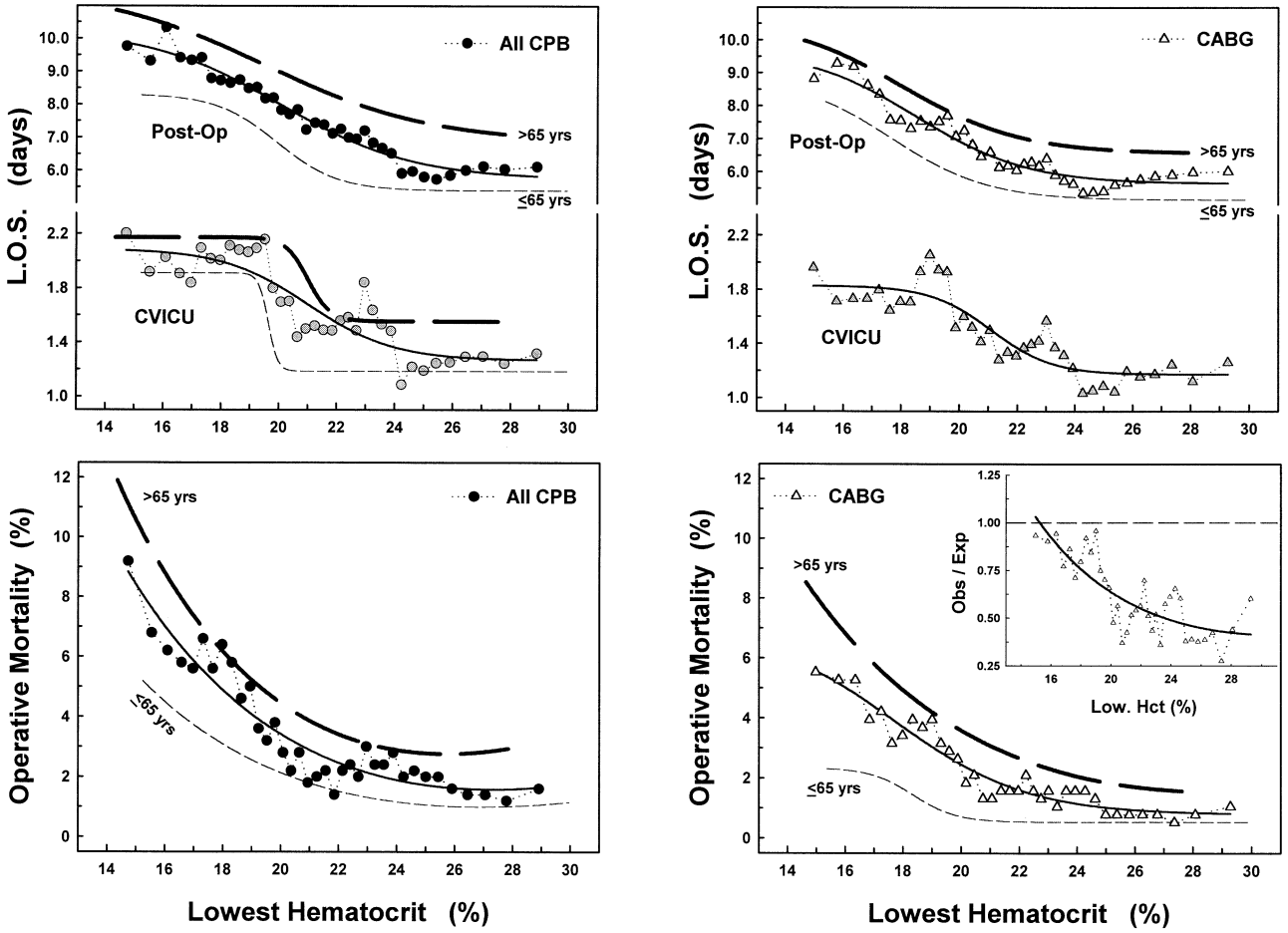

Figure 2. ***Top,*** **CVICU and postoperative hospital stays were systematically and significantly decreased between low (15%) and high (29%) lowest hematocrit overlapping decile groups for all CPB patients (*left*) and for isolated CABG (*right*).** ***Bottom,*** **Operative mortality (OM) was systematically and significantly decreased between low (15%) and high (29%) lowest hematocrit overlapping decile groups for all CPB patients (*left*) and for isolated CABG (*right*). Although OM is lower in young (*dashed, thin lines*) compared with older (*dashed, thick lines*) patients, the relative trends of increased deaths with severity of hemodilution were comparable (lowest hematocrit < 20%) irrespective of age.** ***Bottom right (inset),*** **Observed-to-expected (O/E) mortality decreased systematically and substantially for patient cohorts whose lowest hematocrit value was between 15% and 22% and was relatively unchanged for greater values. Expected mortality was derived from patient data using The Society of Thoracic Surgeons CABG multivariate operative risk model.[23].** ***Lines*** **represent nonlinear regression approximations of actual trends shown for rolling decile groups as symbols. These trends were similar in young (*dashed, thin lines*) and old (*dashed, thick lines*) patients. Symbols for age subgroups were omitted for clarity.**

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Other authors[9-11] have suggested a possible link between hemodilution on CPB and worse operative outcomes after CABG but, to our knowledge, no studies have previously reported an association between CPB hemodilution levels and worse longer-term outcomes. Consistent with our data, DeFoe and colleagues[9] reported increased reoperation of bleeding and low cardiac output and in-hospital mortality with increased hemodilution severity. They, however, did not find a systematic increase in stroke. Hardy and coworkers[10] reported increased postoperative renal failure, hemodynamic instability, and death with decreased hematocrit (1) on pump or (2) during the first 24 hours postoperatively. Fang and colleagues[11] used a multivariate analysis that separated low- and high-risk CABG patients and concluded that hematocrit values below 14% in low-risk patients and 17% in high-risk patients are associated with a doubling of the risk of death. A similar variance was also evident by contrasting our LOS (hematocrit and mortality) hematocrit data for young (lower-risk) versus older (higher-risk) patients (Figure 2). These showed that worse outcomes occur at relatively lower hematocrit values

TABLE 5. Predictors of operative mortality and morbidity after CABG by multivariate logistic regression analysis

Outcome/variable	B	SE	Wald statistic	*P* value	OR	95% CI	
						Lower	Upper
Operative mortality							
Lowest hematocrit (%)	−0.147	0.030	24.595	<.001	0.863	0.815	0.915
Age (years)	0.046	0.010	23.410	<.001	1.047	1.028	1.067
Time on CPB (min)	0.015	0.002	43.458	<.001	1.015	1.011	1.020
Ejection fraction (%)	−0.037	0.009	16.210	<.001	0.964	0.947	0.981
Renal failure	1.487	0.362	16.871	<.001	4.425	2.174	9.010
Redo CABG	0.909	0.339	7.206	.007	2.481	1.279	4.831
Chronic lung disease	0.844	0.258	10.687	.001	2.326	1.403	3.861
Cerebrovascular disease	0.637	0.252	6.405	.011	1.890	1.155	3.096
Peripheral vascular disease	0.623	0.265	5.514	.019	1.866	1.109	3.135
CVICU > 2 days							
Lowest hematocrit (%)	−0.084	0.017	27.757	<.001	0.968	0.957	0.980
Age (years)	0.019	0.006	10.687	.001	1.019	1.008	1.031
Time on CPB (min)	0.013	0.002	39.366	<.001	1.013	1.009	1.017
Ejection fraction (%)	−0.031	0.006	24.359	<.001	0.970	0.958	0.982
Renal failure	1.709	0.304	31.506	<.001	5.525	3.040	10.00
Elective	−0.782	0.181	18.640	<.001	0.458	0.321	0.653
Peripheral vascular disease	0.504	0.188	7.176	.007	1.656	1.145	2.392
Postop LOS > 8 days							
Lowest hematocrit (%)	−0.047	0.011	16.908	<.001	0.954	0.933	0.976
Age (years)	0.040	0.004	89.386	<.001	1.041	1.032	1.049
Time on CPB (min)	0.004	0.001	10.116	.001	1.004	1.002	1.007
Renal failure	1.456	0.226	41.380	<.001	4.292	2.755	6.667
Chronic lung disease	0.497	0.117	18.051	<.001	1.642	1.307	2.066
Cerebrovascular disease	0.278	0.112	20.753	.013	1.321	1.060	1.645
Peripheral vascular disease	0.421	0.127	10.925	.001	1.524	1.188	1.957
Ejection fraction (%)	−0.017	0.004	41.380	<.001	0.983	0.975	0.991
Redo CABG	0.959	0.185	26.835	<.001	2.611	1.815	3.745
Elective	−0.327	0.109	9.003	.003	0.721	0.582	0.893

OR, Odds ratio; *CI,* confidence interval; *SE,* standard error; *B,* coefficient in multivariate model.

TABLE 6. Predictors of 0- to 6-year mortality after CABG by multivariate Cox proportional hazard model analysis

Variable	B	SE	Wald statistic	*P* value	Risk ratio	95% CI	
						Lower	Upper
Lowest hematocrit (%)	−0.051	0.016	10.682	0.001	0.95	0.921	0.980
Age (years)	0.049	0.007	53.24	<0.001	1.05	1.036	1.064
Time on CPB (min)	0.011	0.001	66.37	<0.001	1.011	1.008	1.014
Ejection fraction (%)	−0.012	0.005	6.823	0.009	0.988	0.979	0.997
Renal failure	1.279	0.197	42.129	<0.001	3.597	2.439	5.291
Chronic lung disease	0.383	0.132	8.466	0.004	1.466	1.134	1.901
Cerebrovascular disease	0.593	0.13	20.753	<0.001	1.808	1.403	2.336
Peripheral vascular Disease	0.288	0.122	5.54	0.019	1.333	1.049	1.695

CI, Confidence interval; *SE,* standard error; *B,* coefficient in multivariate model.

in young (20%) compared with older (22% to 24%) patients indicating a varying tolerance of hemodilution on CPB.

In this series, we report associations between hemodilution levels and a large number of complications, as well as a number of morbidity and mortality measures. An obvious reason for this is that more outcome variables were included in the analysis. We also contend that this was facilitated by the consideration of lowest hematocrit as a continuous variable as opposed to use of arbitrary hematocrit values to define patient cohorts. Also, via the overlapping deciles analyses one is able to better define the continuous relations between on-pump hemodilutional anemia and specific postoperative complications, resource use, and death.

Roach and colleagues[12] recently reported that adverse neurologic events of varying severity are unfortunately

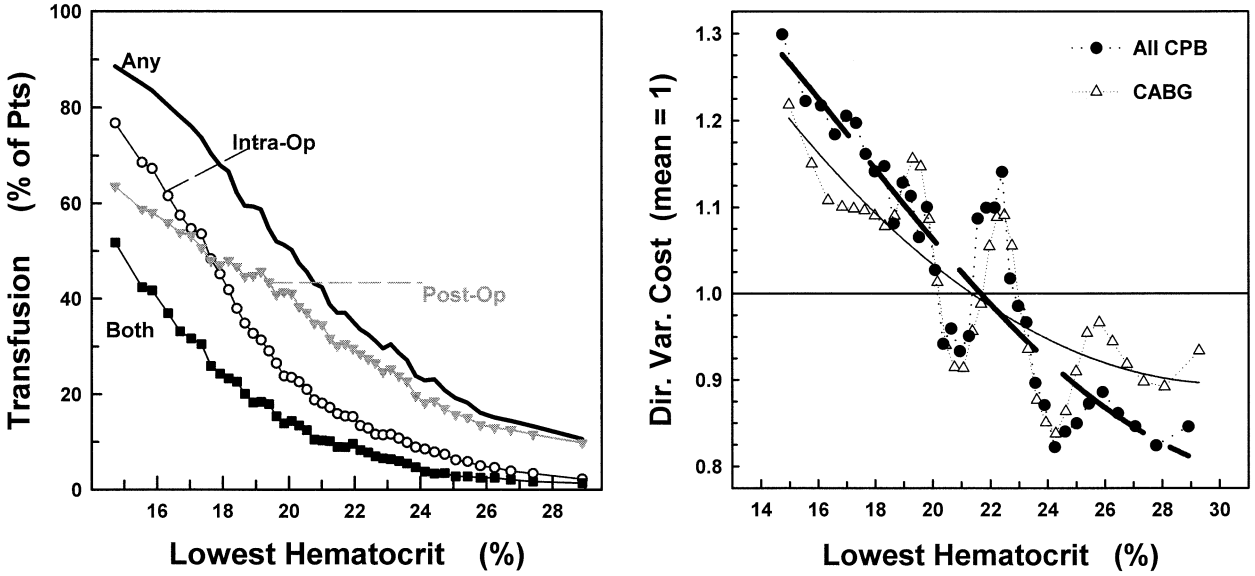

Figure 3. ***Right,*** **Cost of cardiac surgery was systematically and significantly decreased between low (15%) and high (29%) lowest hematocrit overlapping decile groups for all CPB patients (*circles*) and for isolated CABG (*triangles*). *Lines* represent nonlinear regression approximations of actual trends shown for rolling decile groups as symbols.** ***Left,*** **Incidence of transfusion (any, intraoperative, postoperative, and both intraoperative and postoperative) decreased substantially and systematically as a function of hemodilution on pump in cardiac surgery patients, as illustrated for overlapping decile cohorts (500 patients each) from low (15%) to high (29%) lowest hematocrit value during CPB. Compared with nontransfused patients (23.2 ± 3.7 [23.2%]), mean (median) lowest hematocrit values were substantially lower for transfused patients (any: 19.2 ± 3.5 [18.8%]; intraoperative: 18.0 ± 3.2 [17.6%]; postoperative: 19.5 ± 3.6 [19.1%]; both: 17.9 ± 3.2 [17.4%]; all with $P < .001$ [unpaired *t* test]).**

among the most frequent complications of CPB. Moreover, Newman and coworkers[13] showed a relatively high prevalence and persistence of neurocognitive deficits after CABG. To our knowledge, the substantial dependence of the incidence of stroke on lowest hematocrit is the first such reported association in adult cardiac surgery. This perhaps implicates hemodilution severity as a primary cause of CPB adverse neurologic effects. Importantly, this agrees with experimental findings of reduced cerebral oxygen delivery[1,14-19] and worse neurologic outcomes[2,3] with low hematocrit on CPB. Indeed, in case of normothermic CPB, Liam and colleagues[19] showed using a dog model that both oxygen delivery and whole body oxygen uptake were reduced when hematocrit values fell below 25%, becoming significant at 18% or below. They further concluded that (1) hematocrit levels above 18% were needed to maintain oxygen delivery and consumption, (2) the critical hematocrit value may be higher for bypass compared with nonbypass hemodilution states, and (3) the critical hematocrit value for the body appears to be higher than that required for the brain during warm bypass, presumably because the brain is more effective at increasing its flow in hemodiluted states. Interestingly, the experimental data of Liam and colleagues[19] agrees with our clinical data, which showed little or no adverse effects of hemodilution when hematocrit values did not fall below the 21% to 22% levels (Figure 2). This critical hematocrit falls within the 25% and 18% hematocrit values identified by them for adequate versus compromised oxygenation, respectively.

A number of large studies have convincingly shown that small size and female (who are small relative to males) patients have worse outcomes of CPB including greater OM.[6,9,10,20-22] We believe that the poor outcomes in these two patient subpopulations are directly linked to their relatively more severe hemodilution during CPB. In this series, OM was significantly greater in female and low-BSA patient subpopulations, both of which were characterized by significantly ($P < .001$) lower nadir hematocrit values on pump: (1) female compared with male patients [OM: 3.3% (39/1175), lowest hematocrit: 18.7 ± 3.9% vs 1.9% (51/2625), 23.1 ± 3.1%] and (2) small-size (BSA ≤ 1.8 m^2) compared with larger-size (BSA > 1.8 m^2) patients [3.9% (33/846), 18.4 ± 3.2% vs 1.9% (57/2954), 22.7 ± 3.9%].

Prolonged time on cardiopulmonary bypass (>100 minutes) and increased age are also established major determinants of increased morbidity and mortality after CABG,[23] a fact confirmed in this series as well. In addition, we have found that severity of hemodilution during cardiopulmonary bypass as defined by the nadir on-pump hematocrit is a strong predictor of increased CABG morbidity (Figures 3

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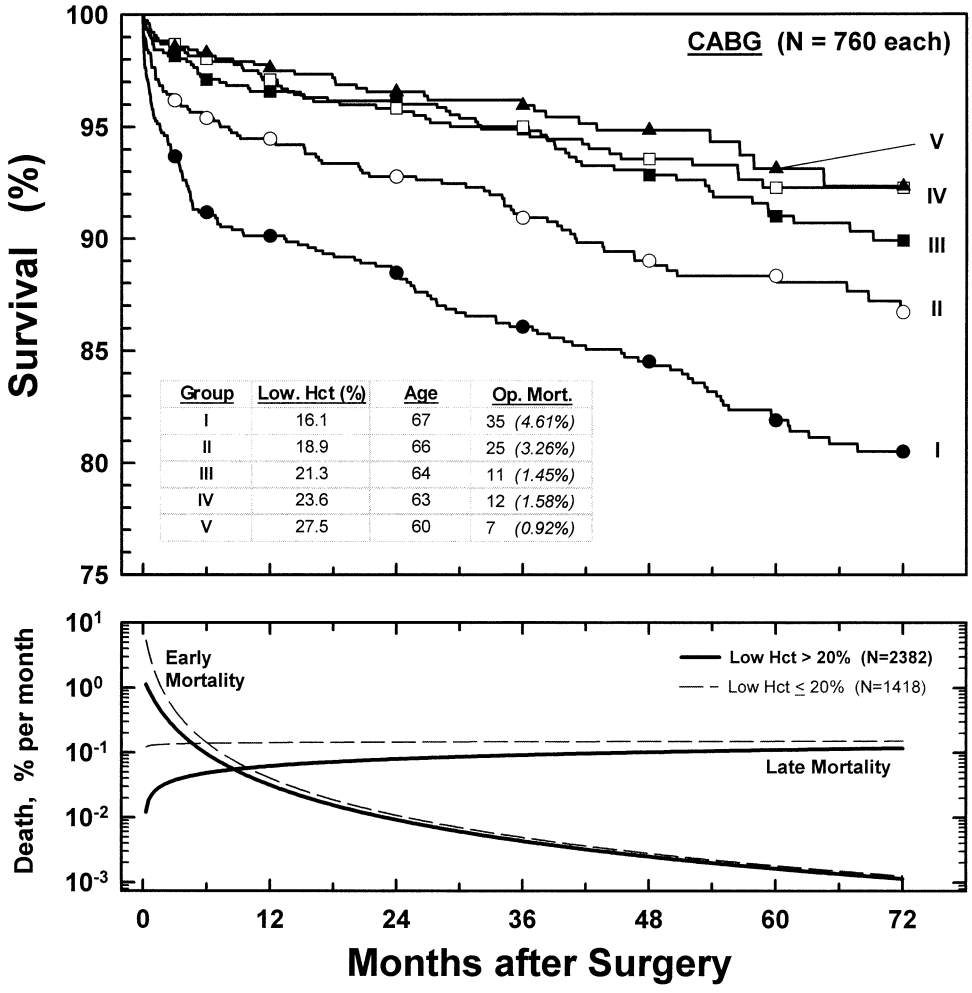

Months after CABG	0	12	24	36	48	60	72
Patients at risk	3800	3703	3256	2824	2269	1743	1177
Survival	100%	95.2%	93.9%	92.5%	90.8%	89.2%	88.1%

Figure 4. ***Top,*** **Kaplan-Meier 0- to 6-year survival plots shown for all five CABG lowest hematocrit quintile groups (I to V: n = 760 each). Compared with quintile V (least hemodiluted), survival for quintiles I ($P < .001$), II ($P < .001$), and III ($P = .002$) was significantly worse by log-rank test.** ***Bottom,*** **Comparison of early and late mortality in CABG patients hemodiluted down to 20% or less versus those with lowest hematocrit values >20% as derived by death hazard analysis. Corresponding survival plots (which are implicit from *top* panel data) are not shown.**

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and 4, Table 5) and mortality (Figure 2, Table 5). Yet, the extent to which hemodilution severity alters observed operative outcomes in relation to patient age and duration of bypass is not known. We thus compared the incidence of OM and postoperative hospital stays (POLOS) in (1) age and (2) time on CPB patient decile groups (380 patients each). Here, within each decile group, OM and POLOS were contrasted for patients whose nadir hematocrit dropped to 21% or less versus those with lowest hematocrit values greater than 21% (Figure 5). Irrespective of age and duration of CPB, we found substantial and systematically increased poorer outcomes (OM and POLOS) in the more hemodiluted patients. Moreover, this hemodilution effect on OM tended to be greater in patients who are over 70 years and/or those who remained on bypass for 2 or more hours. Although it remains to be proven by prospective studies, these findings do suggest that the possibility of improved operative outcomes if hemodilution to levels below 21% is avoided during CPB and that older patients and prolonged cardiopulmonary bypass patients might benefit most from such control of on-pump hematocrit levels. Finally, the tendency of greater OM variance with hematocrit value with

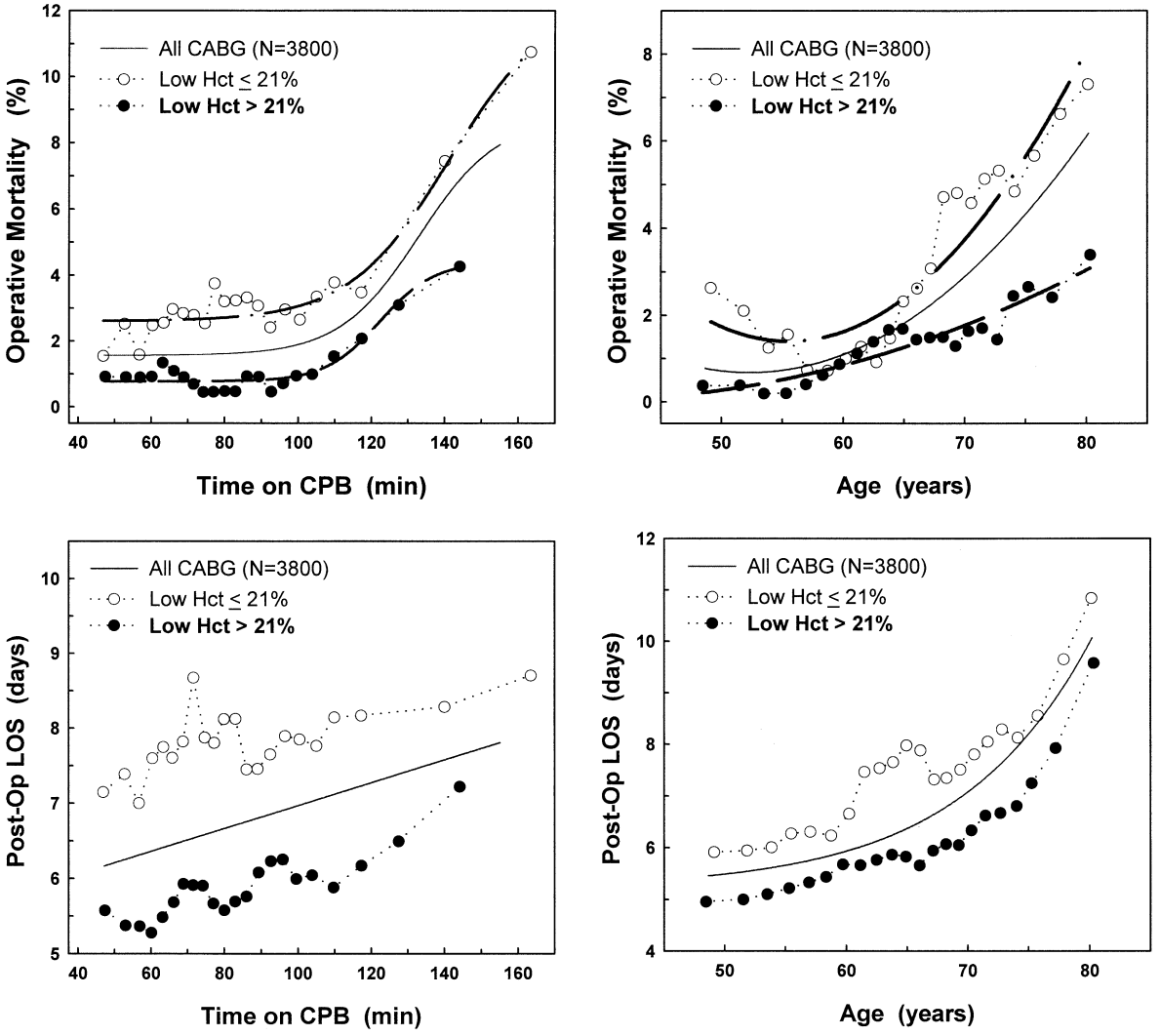

Figure 5. Analysis of the interaction between the effects of lowest hematocrit (symbols) and two important covariate predictors (time on CPB [minutes] and [b] age [years]) of operative mortality (OM) and morbidity represented by postoperative length of hospital stays (postop LOS). *Solid regression lines* were used to delineate the changes in OM and postoperative LOS in terms of the predictor variables time on CPB and age for all patients irrespective of hemodilution levels (symbols were not used for visual clarity). *Dashed lines* in top panels represent regression results describing the (1) OM–time on CPB and (2) OM–age relations for the two hemodilution subgroups. See text for more details.

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longer pump runs is suggestive of a dose effect of on-pump hemodilution (ie, adverse effects of the same low [<21%] nadir hematocrit may be increased as the duration of bypass increases).

If the aforementioned associations between low hematocrit levels on CPB and worse outcomes obtained by the reported univariate and multivariate analyses are shown to be causal by prospective randomized studies, then methods aimed at minimizing on-pump hemodilutional anemia (eg, lowest hematocrit ≥ 22%) might lead to significant improvements in patients at risk. Note, hematocrit value during CPB is an intraoperative variable that cardiac surgeons can potentially control so that adverse outcomes are minimized in contrast to preoperative variables over which they have little or no control and, ironically, these have been traditionally the focus of quality improvement.

Hemodilution during CPB results from the mixing of pump crystalloid and colloid prime solution with the patient's blood, and these two relative volumes, along with pre-CPB hematocrit, will largely determine the nadir hematocrit (Table 2). In that sense, lowest hematocrit value during CPB is then a potentially modifiable risk factor.

Changes to several areas of practice in CPB patients can alter the extent of hemodilution experienced in a given patient. These include controlling preoperative blood loss during routine phlebotomy and cardiac catheterization; possible redesign and use of variable-size, or multiple sizes of, CPB circuits to be used according to patient BSA; minimizing of the tubing size (length and diameter) connecting the patient and pump; more timely return of collected cells to the circulating volumes; more strict control of intraoperative blood loss and fluid administration; use of retrograde autologous priming of the CPB circuit, which has been shown to reduce hemodilution and transfusion requirements[24,25]; and, lastly, freer use of blood transfusions during CPB so as to maintain hematocrit at predetermined levels. The latter is perhaps the most controversial of the above recommendations. Yet, as Figure 3 shows, a large fraction of the more hemodiluted patients are transfused anyway. Moreover, at a minimum, our data raises the prospect that adverse transfusion effects in CPB patients derive, in a significant way, from the associated on-pump hemodilution as opposed to being a consequence of transfusion per se. Obviously, this question will only be resolved by appropriate prospective studies.

In conclusion, we found strong systematic associations between severity of hemodilution on CPB and serious complications affecting most major vital organs; particularly when the nadir hematocrit drops below 22%. Expectedly, these associations then lead to (1) increased resource utilization such as CVICU/hospital stays and operative costs and, more importantly, (2) substantially greater operative mortality. We also found evidence of potential long-term effects of on-pump hemodilutional injury to vital organs as manifested by the worse 0- to 6-year survival due to a sustained increase in death hazard after CPB in the more severely hemodiluted patients. We believe these data represent compelling evidence of substantially greater adverse outcomes when hematocrit value during CPB is allowed to fall below a critical value (~22%) and hence warrant future prospective confirmatory investigation that should also aim to separate the correlated effects of substantial hemodilution on bypass and transfusion of blood products. We further speculate that these adverse effects might have as common mechanisms (1) ischemic vital organ tissue injury within vital organs due to inadequate oxygen delivery at low hematocrits, and (2) systemic inflammatory injury due to increased white cell–endothelial activation in microcirculatory beds of vital organs. These hemodilution effects during CPB per se have been convincingly demonstrated in recent experimental studies by the Boston group[1-3] and by Cook, Daly, and coworkers.[14-16,19]

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